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EXAMINER	
PAK, JOHN D	

ART UNIT	PAPER NUMBER
1616	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/842,547	Applicant(s) Adams et al.
	Examiner John Pak	Art Unit 1616

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *3/25/03 and 4/11/03*

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above, claim(s) *6, 7, 9-12, 14, 15, 20, 21, and 23-29* is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5, 8, 13, 16-19, and 22* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examine

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *15,16*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 1-29 are pending in this application. Claims 9-12, 23-29 are withdrawn from further consideration as being directed to a non-elected invention group. Claims 6-7, 14-15 and 20-21 are withdrawn for examination purposes as being directed to non-elected species. The elected species is GTN. Claims 1-5, 8, 13, 16-19 and 22 are readable on the elected subject matter, and they will presently be examined to the extent that they read on the elected subject matter.

Claims 1-5, 8, 13, 16-19 and 22 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for "inhibiting" malignant cell phenotype in an animal, does not reasonably provide enablement for "preventing" the same. **Additionally,** the specification, while being enabling for inhibiting malignant cell phenotype in an animal for a specific "low dose" range, such as 10^{-14} M to 10^{-10} M, does not reasonably provide enablement for inhibiting malignant cell phenotype with other unspecified "low dose" range. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Lack of Enablement – "preventing": claims 1-5, 13, 16-18

One skilled in the art would be faced with undue experimentation to practice the invention commensurate in scope with the claims. The claims are quite broad. Any nitrogen oxide mimetic for "preventing" any malignant cell phenotype is claimed. The nature of the invention is in the difficult field of treating and "preventing" cancer. The state of the prior art is such that "preventing" cancer has not been successful. The term "preventing" has a meaning that is equivalent to "to keep from happening" or "make

impossible." As thousands of people die each year due to cancer, it is plainly clear that there has been no treatment or protocol that has proven to be effective in "preventing" cancer. While the level of ordinary skill in this field is quite high, given the specialized medical nature of the field, the level of unpredictability in the art (for preventing cancer) is also quite high. No treatment in the world is known to make cancer impossible. While the inventor has shown some evidence that the nitrogen oxide mimetic such as GTN would inhibit malignant cell phenotype such as cancer cells, there is insufficient evidence regarding cancer preventing. There is no working example that shows preventing cancer for an open period of time, e.g. lifetime of an animal, for 10 years, etc. The quantity of experimentation needed to practice the invention as claimed based on the content of the disclosure is extensive and undue. There is no way to know whether the animal subject would respond by "preventing" cancer, except through trial and error. For each different type of animal and malignant cell phenotypes, the skilled artisan would be faced with administering the nitrogen mimetic such as GTN and waiting many years to see if "preventing" is obtained. After all, preventing means to keep malignant cell phenotype such as cancer from happening. Therefore, the scope of the invention directed to "preventing" is not adequately enabled.

Lack of Enablement – "low dose": claims 1-5, 8, 13, 16-19 and 22

The specification, while being enabling for increasing efficacy of an antimalignant modality, treating cancer, or inhibiting malignant cell phenotype in an animal for a specific "low dose" range, such as 10^{-14} M to 10^{-10} M, does not reasonably provide enablement for other unspecified "low dose" range.

The breadth of the claims is quite extensive. The term "low" is a relative one, one that only has meaning when it is known what is meant by "high dose." In the specification, applicant defines "low dose" to mean an amount of nitric oxide mimetic which is capable of increasing, restoring or maintaining a level of nitric oxide mimetic activity to cells which inhibits or prevents malignant cell phenotypes and/or which increases efficacy of an antimalignant therapeutic modality (p. 10, lines 19-24). If there ever were a circular definition this would be it.

Applicant states in the specification that for long term therapy, induction of tolerance against the NO mimetic and side effects become a concern (p. 11, lines 17-20). Applicant apparently believes cardiovascular-treatment amount such as GTN at 0.2 mg/h or greater is high (p. 11, lines 24-28). Applicant states that, in contrast, the "**preferred doses**" are preferably at least 3 to 10,000 fold lower (sentence bridging pp. 11-12). Specification Table 1 additionally provides "examples of various lower preferred doses for nitric oxide mimetics useful in the present invention."

What is not clear from all this is a complete metes and bounds of "low dose." "Preferred" low doses do not fully set forth what is meant by low dose. Preferred doses are usually narrower. Preferred doses do not teach the complete dosing range. While vasodilating amount of GTN may be considered high by applicant, applicant also states that "preferred doses" include a 3 fold lower amount. What does this mean to the skilled artisan? Usually a preferred range is narrower -- hence permitting 3 fold lower in a preferred dose would seem to encompass in a complete dose range an amount that is close or maybe higher than vasodilating, cardiovascular-treatment amounts. The burden is on applicant to provide clear direction and guidance as to suitable dose amounts.

The nature of the invention here is in inhibiting or preventing malignant cell phenotype such as various cancer cells and increasing efficacy of other antimalignant treatments. The state of the art is such that precise dose and protocol are necessary to effectively treat human and animal subjects. As discussed above, higher doses present tolerance and/or side effect problems. There is much research in this field to accurately determine proper dosing range for even proven anticancer drugs. The level of ordinary skill in the field is quite high given its specialized medical nature. Level of unpredictability in the art is quite high given the difficulty in obtaining successful treatments. While applicant has provided some direction and working examples of what is meant by "preferred" low doses, applicant has failed to provide a full range of what is meant by "low dose." When the term "low dose" at a preferred range is close enough to be within 3 fold of a conventional cardiovascular treating amount, one skilled in the art would not be able to determine the metes and bounds of the inventive dosing range (i.e. not just the preferred range) without undue experimentation. Therefore the scope of the invention directed to "low dose" is not adequately enabled.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3, 4 are rejected under 35 U.S.C. 102(a) as being anticipated by Umansky et al. (Intern. J. Oncology, Jan/2000).

Umansky et al. explicitly teach that 0.5 mM GTN induced apoptosis in human breast cancer cell lines derived from primary tumor and from metastasis (p. 109, left column, lines 4-7; p. 110, left column, second full paragraph; p. 111, right column, Figure 1 & first paragraph under "Results").

Low dose issue has already been addressed in this Office Action (pages 4-5), and the discussion there is incorporated herein by reference. It is the Examiner's position that, based on applicant's specification disclosure, the term "low dose" is broad enough to encompass 0.5 mM GTN. Since GTN induces apoptosis, metastases and resistance are not possible (claim 3); the same can be said for development of a more aggressive malignant cell phenotype under any condition (claim 4). The claims are thereby anticipated.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 5, 8, 13, 16-19 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Umansky et al. in view of Bonavida et al. (US 2001/0038832) and Chemical Abstracts 129:36441.

Umansky et al. explicitly teach that 0.5 mM GTN induced apoptosis in human breast cancer cell lines derived from primary tumor and from metastasis (p. 109, left column, lines 4-7; p. 110, left column, second full paragraph; p. 111, right column, Figure 1 & first paragraph under "Results"). Umansky et al. also teach that exposure to

nitric oxide released by GTN triggered apoptosis in human neoplastic lymphoid cells, and human leukemic cells undergo nitric oxide mediated apoptosis (p. 110, left column, second full paragraph). Effective treatment of breast cancer patients is suggested (p. 115, right column, last paragraph).

Bonavida et al. teach that cancer cells which are exposed to NO (nitric oxide), NO donors or mimics undergo rapid programmed cell death (p. 2, paragraph 0016). NO donors or mimics sensitize even resistant tumor cells to endogenous or exogenous agents such as pharmaceutical or radiological cytotoxic agents (p. 3, paragraph 0040). Concentration range of 10-100 micromolar is exemplified for three NO donors (p. 3, paragraph 0046). Another NO donor was used at 1-100 micromolar concentrations (p. 4, paragraph 0049). Human prostate carcinoma cells may be treated with NO and/or NO donors/mimics (p. 4, paragraph 54; claim 5). See also claims 1-20.

Chemical Abstracts 129:36441 teaches 0.012 mg/kg of GTN (nitroglycerin) injection followed by administration of a microsphere and an anticancer drug. Concentration of the anticancer drug is increased.

The difference between the claimed invention and the cited references is that the references do not explicitly disclose in verbatim language each of the claim-specific features, but all such differences are rendered obvious by the combined teachings of the cited references.

- Low dose: Discussion of low dose on pages 4-5 of this Office Action is incorporated herein.. Applicant apparently intends a quite a broad range by "low dose." The cited references disclose or suggest 0.5 mM GTN, 1-100 micromolar NO donors or mimics, and 0.0012 mg/kg GTN. One having ordinary skill in the art would have taken

such teachings and would have been motivated to arrive at a suitably "low dose" of GTN for treatment of malignant cell phenotype such as cancer cells.

- Cells are in a subject at risk for malignant cell phenotype: Nitric oxide mimetic GTN has been shown to be effective in killing cancer cells. Subjects who have cancer are at risk for further malignant cell phenotypes.

- Inhibits development of a more aggressive malignant cell phenotype in the cells upon administration of an anti-VEGF agent:
The cited references teach that GTN induces apoptosis in tumor cells. Apoptosis would then inhibit development of more aggressive malignant cell phenotypes.

- Increasing efficacy of antimalignant therapies against cancer cells:
Bonavida et al. teach that cancer cells which are exposed to NO, NO donors or mimics undergo rapid programmed cell death, and NO donors or mimics sensitize even resistant tumor cells to endogenous or exogenous agents such as pharmaceutical or radiological cytotoxic agents. Chemical Abstracts 129:36441 teaches increasing concentration of anticancer drug at target sites by injecting 0.012 mg/kg of GTN followed by administration of a microsphere and an anticancer drug. Clearly, combined use with other antimalignant therapeutic modalities and increased efficacy are taught.

- Malignant cell phenotype in an animal: Teachings of the cited references suggest treatment of animals with cancer.

- Dependent claim features in claims 16-18: The cited references teach apoptosis and improved treatment when combined with other anticancer therapeutic modalities. Such effects would inhibit metastasis, development of resistance, development of more aggressive malignant cell phenotypes upon administration of anti-VEGF agent, and development of malignant cell phenotype in animals exposed to factors

which lower cellular nitric oxide mimetic activity, because apoptosis causes cell death, which would necessarily bring about all other aforementioned outcomes, and tumor cells would be sensitized by the NO donor/mimic to increase efficacy of another therapeutic regimen.

- Treatment of cancer, prostate cancer to be specific: GTN has been taught to be effective against primary and metastatic breast cancer cells, neoplastic lymphoid cells, leukemic cells, and prostate cancer cells. Treatment of cancer generally, and prostate cancer specifically, has been taught and suggested.

For these reasons, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because the prior art references combined to teach and suggest every element of the invention as well as the claimed invention as a whole.

A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machines are (703) 308-4556 or (703) 305-3592.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Examiner Pak whose telephone number is (703) 308-4538. The Examiner can normally be reached on Monday through Thursday from 8:00 AM to 5:30 PM. The Examiner can also be reached on alternate Fridays.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Mr. Thurman Page, can be reached on (703) 308-2927.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

JOHN PAK
PRIMARY EXAMINER
GROUP 1600